Pestic. Sci. 1998, **53**, 241–244

Insecticidal Properties of Benzofuran-2-carboxylic Acid Derivatives

Yvette A. Jackson,[1*] Mark F. Williams,[1] Lawrence A. D. Williams,[2] Kisha Morgan[3] & Flona A. Redway[3]

[1] Department of Chemistry, University of the West Indies, Mona, Kingston 7, Jamaica, West Indies
[2] Department of Anatomy, University of the West Indies, Mona, Kingston 7, Jamaica, West Indies
[3] School of Natural and Health Sciences, Barry University, 11300 N. E. 2nd Avenue, Miami Shores, FL 33161-6695, USA

(Received 6 May 1997; revised version received 17 December 1997; accepted 9 February 1998)

Abstract: A series of amides and esters of substituted benzo[*b*]furan-2-carboxylic acids have been synthesised, and their activity against adult sweet potato weevils, *Cylas formicarius elegantulus* (Summer) studied. The topical insecticidal potency of these compounds was compared in acetone solution and in a mixture of piperonyl butoxide (PB) and acetone (0·05 + 99·95 by volume). The compounds were much more active when administered in the acetone/PB mixture, and exhibited 48-h LD_{50} values ranging from 1·7 to 26·6 μg per insect. The most active compound, 2-(3,5-dimethylpyrazol-1-ylcarbonyl)-6-methoxy-3-methylbenzofuran, was equiactive with technical grade dimethoate (in acetone/PB) on a weight basis. © 1998 SCI

Pestic. Sci., **53**, 241–244 (1998)

Key words: benzo[*b*]furan-2-carboxylic acid derivatives; insecticidal activity; *Cylas formicarius elegantulus*

1 INTRODUCTION

The sweet potato weevil, *Cylas formicarius elegantulus* (Summer), is one of the most destructive pests of the sweet potato plant (*Ipomoea batatas* (L) Poir.).[1] Larval and adult stages feed on shoots and roots. The insecticidal activity of some 2-carboxylbenzofurans and their coumarin precursors against this pest was first demonstrated by Williams *et al.*,[2] revealing that these compounds were weakly insecticidal when administered in acetone, and that their insecticidal action could be enhanced by piperonyl butoxide (PB), an inhibitor of the mixed function oxidases enzyme system.[3]

When an acetone solution of the ester **1** (Fig. 1)[2] was administered to the sweet potato weevil, it showed a high 48-h LD_{50} of 250·5 μg per insect (Table 1). Our study of derivatives of benzofuran-2-carboxylic acid, especially novel salts of the type **4**, led us to prepare the monomethoxy amides **2**–**7**, and the ester **8**. We studied the action of these compounds on the sweet potato weevil and compared their activity with that of compound **1**.

* To whom correspondence should be addressed.

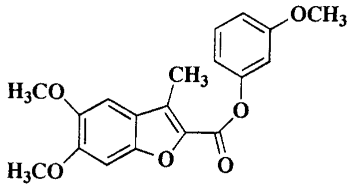
2 METHODS

2.1 Chemistry

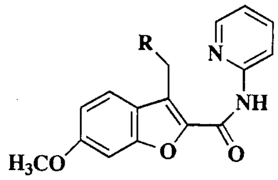
Compound **3** was prepared from compound **2** by bromination with *N*-bromosuccinimide. Cyclization of **3** to **4** was then achieved by refluxing in acetone.[4] The compounds **2, 5, 6, 7** and **8** were synthesized by conversion of the acid **9** to its chloride, and subsequent reaction with the corresponding amino derivative or 2-hydroxypyridine (Fig. 2). The acid **9** was prepared by the action of ethanolic sodium hydroxide on 3-bromo-7-methoxy-4-methylcoumarin.[4]

2.1.1 *General*

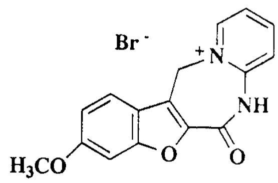
Melting points of all compounds were determined on a Thomas-Hoover melting point apparatus. Infrared



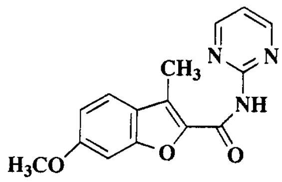
1



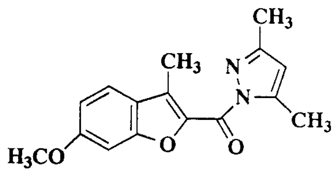
2: R = H
3: R = Br



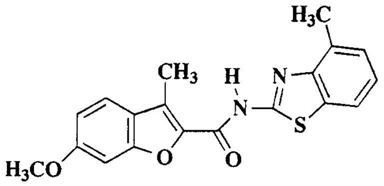
4



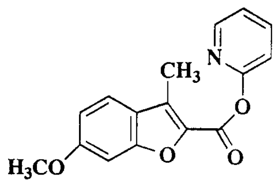
5



6



7



8

Fig. 1. Test compounds.

TABLE 1

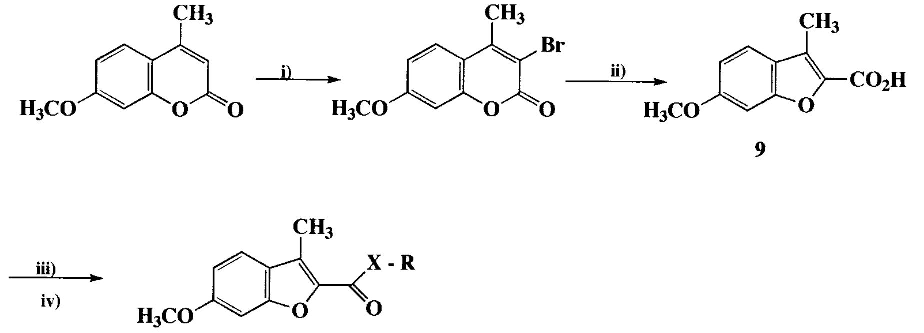
Activity of Benzo[*b*]furan-2-carboxylic acid derivatives against adult *Cylas formicarius elegantulus* by Topical Application of Solutions in Acetone alone or in the Presence of PB Synergist

Compound	LD_{50} (*μg per insect*) *at 48 h with 95% Confidence Interval*[a] (*In acetone*)	(*In PB*/acetone)
1	250·5 (193·3–325·9)	7·31 (5·4–9·6)
2	38·2 (34·8–41·6)	14·4 (10·4–19·0)
3	51·4 (46·8–56·9)	19·3 (15·8–22·7)
4	62·9 (60·0–69·3)	23·1 (18·6–28·7)
5	210·4 (171·1–257·1)	17·3 (12·4–21·6)
6	14·0 (11·6–16·7)	1·7 (0·8–2·9)
7	355·7 (277·6–469·5)	26·6 (21·5–31·9)
8	42·9 (39·0–47·2)	14·04 (11·4–16·8)
Dimethoate[b] (in PB/acetone)		7·8 (5·6–11·4)
Controls		
Acetone	4 μl 0% mortality at 48 h	
PB/acetone[c]	2 μl 0% mortality at 48 h	
	4 μl 15% mortality at 48 h	

[a] $n = 20$, in two replicates of 10 each.

[b] These data correlate with values published by Williams *et al.*[2]

[c] Concentrations of PB represent the lowest and highest values in the solutions applied to the test insect.



9

2, 5-7 : X = NH
8 : X = O

Fig. 2. Synthetic route to benzofuran-2-carboxylic acid derivatives. i) $Br_2/CHCl_3/K_2CO_3$; ii) NaOH/EtOH; iii) $SOCl_2$/py; iv) amine or 2-hydroxypyridine.

spectra were obtained on a Perkin Elmer 735B-model or Perkin Elmer 1600 FTIR spectrophotometer and are for KBr discs. [1H] and [13C]NMR spectra were obtained in deuterochloroform solutions on a 200 MHz Bruker ACE 200 instrument using tetramethylsilane as internal standard. Mass spectral data (chemical ionization) were determined on an ionizing voltage of 70 eV on a Kratos A. E. I. MS-12 spectrometer. Elemental analyses were performed by Medac Ltd, Middlesex, UK. All microanalysis and mass spectral data were in agreement with expected values.

*2.1.2 General procedure for preparation of amides **5**, **6**, **7***

To the dried acid **9** (5·00 g, 24 mmol) was added redistilled thionyl chloride (25 ml) and the mixture heated at gentle reflux for 30 min. Excess thionyl chloride was distilled off. To the residual acid chloride, pyridine (20 ml), followed by the corresponding amine (1·1 mol. equiv.) was added with stirring. This mixture was stirred at room temperature for 48 h, the excess pyridine was removed by evaporation after addition of toluene, and the residue purified by column chromatography (hexane + chloroform, 7 + 3 by volume) to give the desired amide.

2.1.2.1 N-*2-pyrimidinyl-6-methoxy-3-methylbenzofuran-2-carboxamide* (**5**). Pale yellow solid (3·01 g, 44%), m.p. 156–158°C (MeOH). δ_H 2·65 (s, 3H, 3-methyl), 3·92 (s, 3H, OCH_3), 6·95 (m, 2H, H-5 and 7), 7·07 (m, 1H, H-5′), 7·51 (d, 1H, $J = 8$ Hz, H-4), 8·72 (d, 2H, $J = 4$ Hz, H-4′ and 6′), 9·16 (s, 1H, -NH).

2.1.2.2 2-(3,5 dimethylpyrazol-1-ylcarbonyl)-6-methoxy-3-methylbenzofuran (**6**). Brownish-yellow crystals (4·21 g, 61%), m.p. 85–87°C (EtOH). δ_H 2·37 (s, 3H, 3′-methyl), 2·46 (s, 3H, 5′-methyl), 2·60 (s, 3H, 3-methyl), 3·90 (s, 3H, $-OCH_3$), 6·06 (s, 1H, H-4′), 6·95 (d, 1H, $J = 8$ Hz, H-5), 7·07 (s, 1H, H-7), 7·50 (d, 1H, $J = 8$ Hz, H-4).

2.1.2.3 N-*(4-methyl-2-benzothiazolyl)-6-methoxy-3-methylbenzofuran-2-carboxamide* (**7**). Brownish-yellow powder (4·81 g, 56%), m.p. 265–267°C (EtOH). δ_H 2·62 (s, 3H, 3-methyl), 2·70 (s, 3H, 4′-methyl), 3·78 (s, 3H, $-OCH_3$), 6·25 (d, 1H, $J = 2$ Hz, H-5′), 6·90 (dd, 1H, $J = 2$ and 8 Hz, H-5), 7·25 (m, 2H, H-7 and 6′), 7·48 (d, 1H, $J = 8$ Hz, H-4), 7·78 (m, 1H, H-7′).

*2.1.3 2-Pyridyl 6-methoxy-3-methylbenzofuran-2-carboxylate (**8**)*

The procedure as for preparation of amides was followed as detailed above, except that instead of adding 1·1 molar equivs of amine, a corresponding amount of 2-hydroxypyridine was added. At the end of 48 h, work-up and chromatography (hexane + chloroform, 7 + 3 by volume) yielded **8** as a fluffy off-white solid (6·21 g, 90%) m.p. 123–124°C (EtOH). δ_H 2·66 (s, 3H, 3-methyl), 3·88 (s, 3H, $-OCH_3$), 6·95 (dd, 1H, $J = 2$ and 8 Hz, H-5), 7·03 (d, 1H, $J = 2$ Hz, H-7), 7·28 (t, 2H, $J = 4$ and 8 Hz, H-3′ and 5′), 7·54 (d, 1H, $J = 8$ Hz, H-4), 7·86 (dt, 1H, $J = 4$ and 8 Hz, H-4′), 8·48 (d, 1H, $J = 4$ Hz, H-6′).

2.2 Biological testing

2.2.1 Test solutions

Compounds were administered to insects in pure acetone (BDH Ltd) or in a mixture of piperonyl butoxide (PB) (Aldrich Chemical Co.) and acetone (0·05 + 99·95 by volume).

2.2.2 Test insect

C. formicarius were cultured according to Roberts and Williams.[5] Unsexed mature adults weighing 50·0–55·0 mg were used.

2.2.3 Bioassay

Compounds were dissolved in acetone or a PB + acetone mixture (0·05 + 99·95 by volume) at 10 mg ml^{-1}, to produce stock solutions. From each stock solution, 4-μl doses (five to six dose levels) were administered topically to the ventral surface of the abdomen of the test insects, giving 5–100% mortality. Each dose of a compound was evaluated against 20 adult *C. formicarius* in two replicates of 10. The control

insects were treated with 4 μl of pure acetone or 4 μl of the PB + acetone mixture. The number of dead insects was recorded after 48 h.

2.2.4 Statistical analysis

The mortality data (5–100% obtained for five or six concentrations) were analysed using POLO, a DOS-operated version of Finney's Probit Analysis,[6] in order to determine the LD_{50} value (concentrations required to kill 50% of the test insects) for each compound.

3 RESULTS AND DISCUSSION

The order of activity of the compounds **2, 3, 4, 6** and **8** in acetone solution, as judged by their 48-h LD_{50} values (μg per insect), was:- **6** (14·0) > **2** (38·2) > **8** (42·9) > **3** (51·4) > **4** (62·9). These compounds were all more active than compound **1**, which had a 48-h LD_{50} value of 250·5 μg per insect in that medium. Compounds **5** and **7** were not lethal to the insects although compound **5** led to significant paralysis of the treated insects.

The presence of PB in the test medium enhanced the insecticidal activity of all the compounds (Table 1). In PB the order of activity (48-h LD_{50} in μg per insect), of the test compounds was: **6** (1·7) > **8** (14·0) ~ **2** (14·4) > **5** (17·3) > **3** (19·3) > **4** (23·1) > **7** (26·6). In our original study of the benzofurans and their coumarin precursors, PB was seen to have had a similar effect on the activity of these compounds.[2]

Further experiments with other synergists will be performed in future studies in this area.

REFERENCES

1. Sorensen, K. A., Cultural, regulational and educational programmes on the sweet potato weevil in the United States. *Insect. Sci. Applic.*, **8** (1987) 825–30.
2. Williams, L. A. D., Anderson, M. J. & Jackson, Y. A., Insecticidal activity of synthetic 2-carboxylbenzofurans and their coumarin precursors. *Pestic. Sci.*, **42** (1994) 167–71.
3. Bowers, W. S., Phytochemical resources for plant protection. In *Recent Advances in the Chemistry of Insect Control*, ed. N. F. James. Henry Ling Ltd, Dorset, 1984, pp. 272–91.
4. Jackson, Y. A. & Williams, M. F., Novel heterocycles from 2-aminopyridine and derivatives of 3-methylbenzofuran-2-carboxylic acid, *Heterocycles*, **45** (1997) 787–94.
5. Roberts, R. & Williams, L. A. D., Acaricidal and insecticidal activities of three synthetic oxazolidinones. *Pestic. Sci.*, **33** (1991) 393–8.
6. Finney, D. J., *Probit Analysis, a Statistical Treatment of the Sigmoid Response Curve*. Cambridge, 1972, pp. 318–33.